Where is the evidence?
Demonstrating the value of laboratory medicine

Mike Hallworth

International Congress on Quality in Laboratory Medicine

Helsinki, 9 February 2017
Outline

- Introduction
- Understanding value
- Improving outcomes, reducing harm
  (Towards better evaluations)
- Vision and call to action
Importance of lab medicine

- Single highest-volume medical activity
- Patient safety – fast, accurate diagnosis
- Essential to clinically cost-effective delivery of care
- Often the principal basis for costly downstream care
- Spans primary/secondary care
- Added value at pre- & post-analytical phases
Throughput

- Labs
- Medications/other orders
- Inpatient/outpatient/ED visits
- Non-surgical procedures
- Imaging
- Surgical procedures

Ramy Arnaout 2015
Laboratory medicine - cost

- Global IVD market expected to reach $75 bn by 2020, growing at a rate of 5.8% from 2015 to 2020
- 3-5% of healthcare costs
Volume to value

Focus on improving the value of laboratory services
Clinical chemistry

Sample

PROCESS/QUALITY

Result
Integrated value chain
Outline

- Introduction
- Understanding value
- Improving outcomes, reducing harm
- Towards better evaluations
- Vision and call to action
Value can be defined in clinical and economic senses

- Clinical value
  - Diagnostic accuracy
  - Predictive value
  - Clinical utility in decision-making
  - Improved health-related outcomes

- Economic value
  - Economic efficiency and effectiveness compared to standard process of care

*Usually not country or health care system specific*

 Depends on the setting in which the test will be used
The 70% claim

- “70% of critical medical decisions depend on laboratory data”
- “70% of all medical decisions depend on laboratory data”
- “70% of diagnoses depend on laboratory data”
- ............ where is the evidence?
The Value of IVD Testing in Medical Practice

- Rohr UP et al.

- Survey of 79 oncologists/cardiologists:
- “75% of patients underwent IVD testing, testing that led to a substantial clinical decision in 66% of these patients.”
IFCC Task Force on the Impact of Laboratory Medicine on Clinical Management & Outcomes

- Formed May 2012
- Chair M Hallworth
- Objectives:
  - To evaluate the available evidence supporting the impact of laboratory medicine in healthcare
  - To develop the study design for new retrospective and prospective studies to generate evidence-based data to support IFCC promotional activities to the healthcare community and the public

Health outcomes

\[
\text{VALUE} = \frac{\text{Outcome}}{\text{Cost}}
\]

Porter ME: What is value in health care? NEJM 2010; 363: 2477-81
Outcomes research

- Outcomes: “results of medical interventions in terms of health or cost” (Bissell)
  - Clinical
  - Operational
  - Economic
IoM 1999

Health system outcomes
- Safety
- Timeliness
- Effectiveness
- Equity
- Patient-centredness
The need for an outcomes research agenda for clinical laboratory testing
Lundberg G. JAMA 1998; 280: 565-6

“clinicians and laboratorians should all be concerned about the effects of that laboratory test and whether the performance of it was useful for the patient or for the public’s health,”
Evaluation of diagnostic tests

- Technical efficacy
- Diagnostic accuracy
- Diagnostic decisions
- Therapeutic decisions
- Patient outcomes
- Economic evaluation

Effectiveness
Efficiency
Efficacy

Chain of inquiry for valuation of lab tests (The Lewin Group)

<table>
<thead>
<tr>
<th>Technical validity</th>
<th>Clinical validity</th>
<th>Clinical utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to measure the analyte accurately and reliably</td>
<td>Ability to detect and predict the disorder that is associated with an analyte measurement</td>
<td>Clinical effectiveness – the balance of risks and benefits associated with using the test in routine practice</td>
</tr>
<tr>
<td><strong>Accuracy</strong> – analytical specificity</td>
<td>Clinical sensitivity</td>
<td>Intermediate/surrogate outcomes</td>
</tr>
<tr>
<td><strong>–</strong> analytical sensitivity</td>
<td>Clinical specificity</td>
<td>Health outcomes (mortality, morbidity, quality of life)</td>
</tr>
<tr>
<td><strong>Precision</strong></td>
<td>Positive predictive value</td>
<td>Adverse effects of diagnostic use</td>
</tr>
<tr>
<td><strong>Robustness</strong></td>
<td>Negative predictive value</td>
<td>Adverse effects of treatment</td>
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</tbody>
</table>
Value

Value = Delivered **benefits** – delivered **harm**
(undesirable effects of testing)

Epner PL, Gans JE, Graber ML
When diagnostic testing leads to harm: a new outcomes-based approach for laboratory medicine.
Outline

- Introduction
- Understanding value
- Improving outcomes, reducing harm
- Towards better evaluations
- Vision and call to action
Improving lab performance

- Quality assurance ✓
- Standardization/harmonization ✓
- Process optimization ✓
- Method development ✓
- Reference intervals ✓
- Outcome studies ??
Outcome studies differ from studies of prognostic accuracy

- Studies of prognostic accuracy ask: “Does the result of the test predict an outcome of interest?”
- Outcome studies ask: “Is the use of the test associated with improved outcomes?”
High sensitivity TnI on presentation enables early safe discharge

- Admission hs-cTnI of 1.9 ng/L (Architect) used to stratify patients:
  - ≤1.9: discharge unless high-risk of ACS or sample taken within 1h of pain
  - >1.9: admit to CDU for 2nd cTnI
- Admissions fell from 60.9% to 38.4%
- Mean LOS fell from 23h to 9.6h
- Follow up:
  Negative Predictive Value for major adverse cardiac event:
  - at 30 days = 99.6%
  - at 9 months = 98.4%

Ford, C: personal communication 2016
Challenge: Connecting Laboratory Testing to Outcomes

Lab Test → Clinical Decision

Diagnosis → Health-Related Outcomes

Treatment → Health-Related Outcomes

Demonstrating the value of lab tests on health outcomes is reliant on linking the test with processes that directly impact outcomes.

(R. Christensen)
The problem with getting evidence of added value

“In order to improve outcomes, a laboratory test must be appropriately ordered, conducted, returned with results on a timely basis, correctly interpreted and affect a decision for further diagnosis and treatment”

Lewin Group report on The Value of Laboratory Screening and Diagnostic Tests for Prevention and Health Care Improvement, 2009
To demonstrate the link between a testing strategy and an outcome:

- The test needs to be used appropriately – better utilization, communication and interpretation
- The study design must be rigorously defined and properly implemented – better evaluations related to specific clinical decisions
Medical error in the US

- Estimated 251,454 deaths 2013

- Compare: (CDC data for 2013)
  - 611,105 deaths from cardiac disease
  - 584,881 deaths from cancer
  - 149,205 deaths from chronic respiratory disease

Makary MA, Daniel M (JHMI): *BMJ* 2016;353:i213929
Diagnostic error

- Estimated 5% of US adults seeking OP care each year experience a diagnostic error
- Contribute approx 10% of patient deaths and 6-17% of adverse events in hospitals

(Improving Diagnosis in Health Care, Health & Medicine Division, National Academies 2015)
Diagnostic Error

- Diagnostic errors are defined as misdiagnosis, missed diagnosis, or delayed diagnosis\(^1\)

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P. Epner
Lab-related causes of diagnostic error

- Inappropriate test ordered (overuse)
- Appropriate test not ordered (underuse)
- Appropriate test result misapplied
  - Knowledge deficit
  - Failure of synthesis
  - Misleading result
- Appropriate test result delayed/missed
- Appropriate test result inaccurate

(Epner et al BMJ Qual Saf 2013)
Faulty process leading to missed diagnosis:

- Failure to order diagnostic/lab test: 55%
- Inappropriate/inadequate follow-up: 45%
- Failure to obtain adequate history/exam: 42%
- Incorrect interpretation of diag test: 37%
- Failure to refer: 26%
- Provider did not receive test results: 13%
- Tests ordered but not done: 9%
- Tests performed incorrectly: 8%
Improving diagnosis and reducing diagnostic errors: *the next frontier of laboratory medicine*

Plebani M, Lippi G
Lab-related causes of diagnostic error

- Inappropriate test ordered
- Appropriate test not ordered
- Appropriate test result not used properly
  - Knowledge deficit
  - Failure of synthesis
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- Appropriate test result wrong/inaccurate

(Epner & Astion, 2012)
Systematic reviews

- Van Walraven (1998)
  - JAMA 280; 550-558
  - Rates of inappropriate testing 4-95%

- Zhi et al (2013)
  - 1997-2012
  - 34,009 citations
  - 493 selected for review
  - 42 included in review
Useful definitions

1. **Utilization**: The number of tests ordered
2. **Appropriateness**: the fraction ordered *correctly*
3. **Overuse**: the fraction ordered *incorrectly*
4. **Underuse**: the fraction of tests that *should have been* ordered that were ordered

Ramy Arnaout
42 studies
- 38 investigated overuse
- 8 investigated underuse
- 4 both

31 objective/11 subjective criteria
20 looked at >1 test
Zhi et al (2013)

- Overall mean rate of inappropriate overuse = 20.6% (95% CI 16.2 – 24.9%, n=114)

- Overall mean rate of underuse = 44.8% (95% CI 33.8-55.8%, n= 18)
Results: overuse vs. underuse

Note, *P*-values uncorrected for multiple possible binnings

Zhi et al, 2013
Preventing overdiagnosis

- “Medicine’s much-hailed ability to help the sick is fast being challenged by its propensity to harm the healthy”
- “Too many people are being overdosed, overtreated and overdiagnosed”
  Moynihan et al, BMJ 2012
Dangers of overuse

- 5% of healthy patients get abnormal test results
- “False findings” or irrelevant abnormalities can lead to unnecessary further testing and expensive and potentially risky interventions
More sensitive tests

- Ability to detect smaller abnormalities increases prevalence of disease (Black, 1999)

- More sensitive tests allow diagnosis of less severe forms of disease/disorder - hsTrop

- Requires care and thought about use of labels, and when we use therapeutic approaches designed for more serious illness
Lab-related causes of diagnostic error

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- Appropriate test not ordered
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(Epner & Astion, 2012)
Do users understand tests?

- Primary Care Physicians’ Challenges in Ordering Clinical Laboratory Tests and Interpreting Results
  
  *JABFM 2014; 27: 268-274*

- Physicians order tests in 31% of patient encounters

  - **14.7%** report uncertainty about ordering
  - **8.3%** report uncertainty about interpreting
UK junior hospital doctors: “How confident are you in requesting laboratory tests?”

(Khromova & Gray, 2008)
Goal 2:
Enhance health care professional education and training in the diagnostic process
- Appropriate use of diagnostic tests
Potassium reference ranges
(data from UK Pathology Harmony)
Reference range harmonization

- UK Pathology Harmony project
  - www.pathologyharmony.co.uk

- Pediatrics – CALIPER
  (CAAnadian Laboratory Initiative in PEEdiatric Reference intervals)

  “Closing the gaps in Pediatric Laboratory Reference Intervals: A CALIPER Database of 40 Biochemical Markers in a Healthy and Multiethnic Population of Children”

  Clin Chem 2012: 58; 854-868
Lab-related causes of diagnostic error

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(Epner & Astion, 2012)
ECRI Institute’s Top 10 Patient Safety Concerns for 2014

1. Data integrity failures with health information technology systems*
2. Poor care coordination with patient’s next level of care
3. Test results reporting errors
4. Drug shortages
5. Failure to adequately manage behavioral health patients in acute care settings
6. Mislabeled specimens
7. Retained devices and unretrieved fragments*
8. Patient falls while toileting
9. Inadequate monitoring for respiratory depression in patients taking opioids
10. Inadequate reprocessing of endoscopes and surgical instruments*
## International Health Rankings
(Commonwealth Fund, 2014)

<table>
<thead>
<tr>
<th></th>
<th>AU</th>
<th>CH</th>
<th>CA</th>
<th>DE</th>
<th>FR</th>
<th>NL</th>
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<th>NZ</th>
<th>SE</th>
<th>UK</th>
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<tbody>
<tr>
<td><strong>Overall rank</strong></td>
<td>4</td>
<td>2</td>
<td>10</td>
<td>5</td>
<td>9</td>
<td>5</td>
<td>7</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td><strong>Safe care</strong></td>
<td>3</td>
<td>4</td>
<td>10</td>
<td>6</td>
<td>2</td>
<td>7</td>
<td>11</td>
<td>8</td>
<td>5</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td><strong>$ Per capita 2011</strong></td>
<td>3800</td>
<td>5643</td>
<td>4522</td>
<td>4495</td>
<td>4118</td>
<td>5099</td>
<td>5669</td>
<td>3182</td>
<td>3925</td>
<td>3405</td>
<td>8508</td>
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## Safe Care measures

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<td><strong>Safe care rank</strong></td>
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<td>7</td>
<td>11</td>
<td>8</td>
<td>5</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td><strong>Delayed abnormal results</strong></td>
<td>7%</td>
<td>5%</td>
<td>11%</td>
<td>5%</td>
<td>3%</td>
<td>5%</td>
<td>10%</td>
<td>8%</td>
<td>9%</td>
<td>4%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Incorrect diagnostic test</strong></td>
<td>4%</td>
<td>3%</td>
<td>5%</td>
<td>2%</td>
<td>3%</td>
<td>6%</td>
<td>4%</td>
<td>5%</td>
<td>3%</td>
<td>2%</td>
<td>5%</td>
</tr>
</tbody>
</table>

(Commonwealth Fund, 2014)
Proper systems to ensure results are actioned

- Electronic systems for acknowledgement of results
- Lab follow up of critical results which have not been viewed/actioned
Notification of critical results

“Urgent physician notification of critical results, both qualitative and quantitative, has become the standard of care because of high impact on patient welfare”

Global trends in critical value practices and their harmonization
Kost GJ and Hale KN
Perceptions of missed test results

In the past year I have missed an abnormal result that led to delayed patient care

- Yes (%): 19.2
- No (%): 26.9
- Don't know (%): 53.9

In the past year a colleague has missed an abnormal result that led to delayed patient care

- Yes (%): 38.5
- No (%): 11.5
- Don't know (%): 50
Information overload

- Survey of 2590 primary care physicians
- Median number of alerts (path/Xray) per day: 63
- 86.9% felt number of alerts excessive
- 69.6% reported more alerts than they could effectively manage
- 29.8% reported having missed results leading to care delays

Singh et al. JAMA Intern Med 2013; 173: 702-4
# Alert thresholds

<table>
<thead>
<tr>
<th>Evidence level</th>
<th>Na- low</th>
<th>Na- high</th>
<th>K- high</th>
</tr>
</thead>
<tbody>
<tr>
<td>4: Individual institutions</td>
<td>115-125</td>
<td>150-160</td>
<td>6.0-7.0</td>
</tr>
<tr>
<td>3: Surveys of labs/clinicians</td>
<td>120-125</td>
<td>155-160</td>
<td>6.0-6.5</td>
</tr>
<tr>
<td>2: Prof. body recommendations</td>
<td>120</td>
<td>155-160</td>
<td>6.0-6.5</td>
</tr>
<tr>
<td>1: Clinical outcome studies</td>
<td>120</td>
<td>155</td>
<td>6.2-7.0</td>
</tr>
</tbody>
</table>

What alert thresholds should be used to identify critical risk results: a systematic review of the evidence. 
Resources

- CLSI Guideline GP47: “Management of Critical- and Significant-Risk Results”
  December 2015
  http://shop.clsi.org/GP47.html

- NHS England: “Standards for the communication of patient diagnostic tests on discharge from hospital”
  March 2016
Outline

- Introduction
- Understanding value
- Improving outcomes, reducing harm
- Towards better evaluations
- Vision and call to action
Components of test evaluation

- Analytical performance
- Clinical performance
- Clinical effectiveness
- Cost effectiveness
- Impact of testing on patient, organization, society

Outline

- Introduction
- Understanding value
- Improving outcomes, reducing harm (Towards better evaluations)
- Vision and call to action
The vision

- 21st century medicine needs a flexible information resource:
  - that facilitates selection of the right test on the right patients at the right time,
  - with results delivered in a timely fashion to the right place
  - accompanied by context-specific interpretation
  - linked to guidance on agreed action to be taken (where appropriate)
  - with validated patient-oriented clinical and economic outcome measures
Call to action...

- Agree definition and validation of effectiveness measures – a “common currency” for outcomes

- Benchmark existing and new biomarkers in specified situations using commonly accepted measures of clinical effectiveness

- Improve utilization of new and existing biomarkers –
  - optimum testing strategies based on presenting complaint
  - support of effective requesting
  - timely and appropriate result transmission
  - availability of consultation and interpretation
  - audit of effectiveness in practice – *work your data*
Improving diagnosis

**Recommendation 1:**
- health care organizations should ensure that health care professionals should have the appropriate knowledge, skills, resources and support to engage in teamwork in the diagnostic process...
“Here is our opportunity to be welcomed as participants in the diagnostic process. The [IoM] committee is saying, it’s time for you to suit up. The score is tied 3-3 in the bottom of the ninth, and we’re sending the pathologist to the plate. Don’t strike out. You’re going to have to swing the bat”

Mike Laposata (Galveston)

CLN January 2016
Changing role of lab medicine

- From:
  - Specimen-centred
  - Clinical testing
  - Lab. performance
  - Provider of results

- To:
  - Patient-centred
  - Clinical decision-making
  - Patient outcomes
  - Partner in care
The future...

- “Never make predictions, especially about the future...”
  Yogi Berra

- “The best way to predict the future is to shape it”
  Willi Brandt
References

- Special issue eJIFCC January 2015
  www.ifcc.org

- IFCC Task Force report
  “Current Evidence and Future Perspectives on the Effective Practice of Patient-Centered Laboratory Medicine”: Hallworth MJ et al.
  Clinical Chemistry 2015 ;61;589-599